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**Organic & Biomolecular Chemistry**

**PAPER**

### γ-Sultam-cored N,N-ligands in ruthenium(II)-catalyzed asymmetric transfer hydrogenation of aryl ketones†

Slavko Rast, a Barbara Modec, b Michel Stephan a,c and Barbara Mohar a

The synthesis of new enantiopure syn- and anti-3-(α-aminobenzyl)benzo-γ-sultam ligands 6 and their application in the ruthenium(II)-catalyzed asymmetric transfer hydrogenation (ATH) of ketones using formic acid/triethylamine is described. In particular, benzo-fused cyclic ketones afforded excellent enantioselectivities in reasonable time employing low loading of the syn ligand-containing catalyst. A never-before-seen dynamic kinetic resolution (DKR) during reduction of a γ-keto carboxylic ester (S7) derivative of 1-indanone is realized leading as well to excellent induction.

### Introduction

The efficient asymmetric transfer hydrogenation (ATH) of ketones employing the HCO$_2$H/Et$_3$N binary mixture can be currently achieved under mild conditions by three generations of RSO$_2$-DPEN-based chiral Ru(II) complexes (available in both enantiomeric forms, DPEN = trans-1,2-diphenylethylenediamine) (Fig. 1)."1–5 Noyori and co-workers' chiral [RuCl(TsDPEN)(η$_6$-arene)]-type complexes (1" generation) were the starting point of such catalyzed asymmetric transformation both on the applied and fundamental levels.2,3 Following, intra-covalent tethering of the diamine and η$_6$-arene ligand units (2" and 3" generations) led to an increased longevity of the catalytic species improving thus the turnover number.4,5

![Fig. 1 "SO$_2$DPEN"-Embedded ATH-efficient chiral Ru(II) complexes.](image)

Exploring the origin of the stereocontrol by the structural stereoarray of the 1" generation ligands and aiming to enhance the enantioselectivity and catalyst activity, empirical modifications of the chiral elements were undertaken (Fig. 2). In particular, TsDPEN skeletal alteration at the level of its ethylene-bridge substituents on position 1 or 2 revealed the critical importance of their aromatic nature (and inherent steric bulk) as well as the advantage of their *anti* disposition.2,6

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† Electronic Supplementary Information (ESI) available: X-ray crystallographic data for racemic trans-5, [syn-(3S,1'R)-6] (S)-CSA, [anti-(3S,1'R)-6] (S)-CSA, and S7 ATH major reduction product, HPLC and GC chromatograms of ATH products, $^1$H, $^{13}$C NMR and HMBC spectra. See DOI: 10.1039/x0xx00000x

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in our ongoing research interest in this area, we present hereafter the synthesis of 5-membered cyclic minimalistic TsDPEN analogs (Fig. 3) and their investigation in the ATH of various classes of ketones. This new design possesses a partial degree of stereochemical rigidity, maintaining however TsDPEN structural elements of the vic-diaryl disposition and the mono N-sulfonyl group. Such structure gives rise to two possible pairs of syn and anti diastereomers which preparation was targeted.

Results and discussion

Synthesis of the New 5-Membered Cyclic N,C-SO2-DPEN Ligands. In this study, we opted for a non-asymmetric synthetic strategy emphasizing on a convenient access to these ligands with a late-stage resolution. Thus, the NaOMe-mediated Wittig reaction of sodium ortho-formylbenzenesulfonate with benzyltriphenylphosphonium chloride afforded pure sodium (E)-3-styrylbenzenesulfonate ([E]-1) in 59% yield after recrystallization (Scheme 1). Conversion into the (E)-sulfonamide (E)-2 followed by epoxidation with m-CPBA and reaction with LiOMe in MeOH led to the regioselective formation of the 6-endo-tet-cyclized trans-δ-sultam trans-4 in high overall yield (82%). Such regioselectivity is supported by 1H,13C-HMBC analysis from a correlation between the proximal aromatic hydrogen of the 1,1-dioxo-benzo-1,2-thiazinane core and the carbon atom bearing the hydroxyl group (see the Supporting Information).7 Tandem in situ O-mesylation–intra-N-alkylation furnished in 76% yield the trans-configured aziridine-cored product trans-5 (for its X-ray structure showing the aromatic rings in trans and a chiral angular N atom, see the Supporting Information). Alternatively to this circuitous approach, a straightforward single-step conversion of (E)-2 into trans-5 via Rh4(OAc)12-catalyzed aziridination using Phl(OAc)2 was achieved in 57% yield. Further on, consecutive aziridine highly regioselective ring-opening with sodium azide in MeCN/H2O (4:1) and Pd/C-catalyzed hydrogenation gave the syn-3-((α-aminobenzyl)-benzo-γ-sultam syn-6. The (3S,1R)- and (3R,1S)-configured enantiomeric ligands 6 were separated by preparative chiral HPLC in >99% ee and 78% combined yields. The absolute configuration of the 1'R eluting enantiomer was determined by X-ray of its (S)-CSA salt (Fig. 4).9

In our ongoing research interest in this area, we present hereafter the synthesis of 5-membered cyclic minimalistic TsDPEN analogs (Fig. 3) and their investigation in the ATH of various classes of ketones. This new design possesses a partial degree of stereochemical rigidity, maintaining however TsDPEN structural elements of the vic-diaryl disposition and the mono N-sulfonyl group. Such structure gives rise to two possible pairs of syn and anti diastereomers which preparation was targeted.

![Fig. 2](image-url) Possible heterocyclic regioisomers of "structurally-simplified TsDPEN".

![5-Membered N,C-SO2-DPEN](image-url)

![6-Membered N,C-SO2-DPEN](image-url)
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**Scheme 1** Preparation of the syn-3-(α-aminobenzyl)-benzo-γ-sultam ligand 6 enantiomers.

Next, the complementary diastereomer anti-3-(α-aminobenzyl)-benzo-γ-sultam anti-6 was prepared analogously, however by resorting to NaHMDS as the base in the Wittig step (Scheme 2). The resulting ~1:1 (E/Z)-isomeric mixture 1 was directly engaged in the further transformation (via the sulfonamide 2) into the aziridine 5 upon Rh₂(OAc)₄-catalyzed aziridination. The cis and trans diastereomers 5 were separated by silica gel chromatography at this stage of the sequence (28% yield for cis-5) and the former was converted as above into the corresponding racemic anti-3-(α-aminobenzyl)-benzo-γ-sultam anti-6. Its (3S,1'R)- and (3R,1'S)-configured enantiomers were separated by preparative chiral Supercritical Fluid Chromatography (SFC) affording the ligands in >99% ee and 44% combined yields. The absolute configuration of the 1ˢᵗ eluting enantiomer was equally determined by X-ray of its (S)-CSA salt (Fig. 5).¹¹
Evaluation of the New Sulfonamido–Amine Ligands 6 in ATH. The assessment of the efficiency in ATH of the Ru(II) complexes incorporating the new 3-(α-aminobenzyl)-benzo-γ-sultam ligands was first conducted on the representative benchmark substrates acetophenone (S1), ethyl benzoyleacetate (S2), 1-indanone (S3), and α-tetralone (S4) (Table 1). The Ru complexes were prepared from [RuCl3(η5-arene)]2 precursor and the enantiopure sulfonamido–amine ligand 6 (syn or anti; 1.1 equiv to Ru atom) at 40 °C (1 h) in 1,2-dichloroethane. The catalysts’ screening with an S/C = 200 was performed at 40 °C using HCO2H/Et3N 5:2.

The outcome of this exploratory profiling clearly revealed the faster reduction rate using the new sulfonamido–amine ligands 6 versus the more flexible TsDPEN and “altered TsDPEN” ligands, or Wills’ conformationally locked indane-cored sulfonamido–amine ligands of Fig. 2. Also, it was noticed for TsDPEN that supplemental amount of HCO2H/ Et3N 5:2 was required in order to revitalize the reduction and drive it to completion. However, acetophenone (S1) and its α-ethoxycarbonyl-substituted derivative S2 afforded lower enantioselectivities (up to 85% ee and 92% ee, respectively) to the ones with the TsDPEN reference. Noteworthy, as (R)-1-phenylethanol was the major resulting enantiomer, the sense of induction on acetophenone (S1) of the syn-(3R,1’S)-6 and anti-(3R,1’R)-6 revealed to be in line with the one expected with the syn-(1R,2S)-TsDPEN (as its syn-(1S,2R)-enantiomer led to (S)-1-phenylethanol) or observed with anti-(R,R)-TsDPEN (Fig. 2).

Noticeably, the performance of syn-(3R,1’S)-6 was particularly good against the benzo-fused ketones, 1-indanone (S3) and α-tetralone (S4), as up to 99% ee with full conversion was obtained in reasonable times leading as well to (R)-configured alcohols. Also, (R)-configured products (95 to >99% ee) were formed employing the anti-(3R,1’R)-6 demonstrating hence that the chirality on the C(3) atom (bearing the sulfonamido group) predominantly determines the enantiofacial discrimination.
Table 1 Ru(II)-catalyzed ATH of benchmark ketones with the enantiopure ligands syn-(3R,1'S)-6 (HPLC 2NS eluting) and anti-(3R,1'R)-6 (SFC 1NS eluting)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Ligand</th>
<th>(\eta^6)-arene</th>
<th>t (h)</th>
<th>Conv. (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>syn-6</td>
<td>p-cymene</td>
<td>4</td>
<td>&gt;99</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3\textsuperscript{a}</td>
<td>100</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>syn-6</td>
<td>mesitylene</td>
<td>7</td>
<td>80</td>
<td>72</td>
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<tr>
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<td>p-cymene</td>
<td>4</td>
<td>&gt;99</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>anti-6</td>
<td>mesitylene</td>
<td>7</td>
<td>90</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>TsDPEN</td>
<td>p-cymene</td>
<td>4\textsuperscript{b}</td>
<td>25</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7\textsuperscript{b}</td>
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<td>99</td>
<td></td>
</tr>
<tr>
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<td>p-cymene</td>
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<td>mesitylene</td>
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<td>86</td>
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<td>p-cymene</td>
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<tr>
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<td>p-cymene</td>
<td>7</td>
<td>85</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7\textsuperscript{b}</td>
<td>&gt;99</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>S3</td>
<td>syn-6</td>
<td>p-cymene</td>
<td>4</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>anti-6</td>
<td>mesitylene</td>
<td>7</td>
<td>90</td>
<td>95</td>
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<tr>
<td></td>
<td>TsDPEN</td>
<td>p-cymene</td>
<td>4\textsuperscript{a}</td>
<td>50</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20\textsuperscript{b}</td>
<td>&gt;99</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>S4</td>
<td>syn-6</td>
<td>p-cymene</td>
<td>3</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mesitylene</td>
<td>7</td>
<td>80</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>anti-6</td>
<td>p-cymene</td>
<td>7</td>
<td>95</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>anti-6</td>
<td>mesitylene</td>
<td>7</td>
<td>85</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>TsDPEN</td>
<td>p-cymene</td>
<td>3</td>
<td>25</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3\textsuperscript{a}</td>
<td>40</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20\textsuperscript{b}</td>
<td>98</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: S/C = 200, ketone (1.0 mmol), 1,2-dichloroethane (1 mL), HCO\textsubscript{2}H\textsubscript{2}N\textsubscript{5:2} (250 \mu L), 40 °C. Conversion was determined by \textsuperscript{1}H NMR of the extracted crude. Isolated yields were 96–98%. Ees were determined by chiral GC or HPLC. (R)-Configured alcohols were obtained in all cases. For further details, see the Experimental Section. \textsuperscript{b} Reaction in neat HCO\textsubscript{2}H\textsubscript{2}N\textsubscript{5:2} (500 \mu L).

Therefore, the [RuCl\textsubscript{2}(p-cymene)]\textsubscript{0}/(3R,1'S)-6 complex was further screened on a series of methoxycarbonyl substituted 1-indanone (S6–S7) and methoxycarbonyl substituted \(\alpha\)-tetralone (S8–S10) (Table 2).

Table 2 Ru(II)-catalyzed ATH of benzo-fused cyclic ketones with the syn-(3R,1'S)-6 (HPLC 2NS eluting) ligand\textsuperscript{a}

<table>
<thead>
<tr>
<th>Ketone</th>
<th>S/C</th>
<th>t (h)</th>
<th>Conv. (%)</th>
<th>cis/trans</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3</td>
<td>1000</td>
<td>16</td>
<td>95</td>
<td>-</td>
<td>99</td>
</tr>
<tr>
<td>S4</td>
<td>1000</td>
<td>16</td>
<td>&gt;99</td>
<td>-</td>
<td>99</td>
</tr>
<tr>
<td>S5</td>
<td>1000</td>
<td>12</td>
<td>100</td>
<td>-</td>
<td>99</td>
</tr>
<tr>
<td>S6</td>
<td>200</td>
<td>4</td>
<td>100</td>
<td>97:3</td>
<td>&gt;99 (cis)</td>
</tr>
<tr>
<td>S7</td>
<td>200</td>
<td>6</td>
<td>100</td>
<td>95:5</td>
<td>&gt;99 (trans)</td>
</tr>
<tr>
<td>S8</td>
<td>200</td>
<td>6</td>
<td>&gt;99</td>
<td>98:2</td>
<td>&gt;99 (cis)</td>
</tr>
<tr>
<td>S9</td>
<td>100</td>
<td>6</td>
<td>&gt;99</td>
<td>50:50</td>
<td>99 (cis)</td>
</tr>
<tr>
<td>S10</td>
<td>200</td>
<td>3</td>
<td>100</td>
<td>&gt;99 (cis)</td>
<td>&gt;99 (trans)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: [RuCl\textsubscript{2}(p-cymene)]\textsubscript{0}/(3R,1'S)-6, ketone (1.0 mmol), 1,2-dichloroethane (1 mL), HCO\textsubscript{2}H\textsubscript{2}N\textsubscript{5:2} (250 \mu L), 40 °C. Conversion and cis/trans ratio (dr) were determined by \textsuperscript{1}H NMR of the extracted crude. Isolated yields were 94–99%. Ees were determined by chiral GC or HPLC. (R)-Configured alcohols were obtained in all cases. For further details, see the Experimental Section. \textsuperscript{b} Determined by \textsuperscript{1}H NMR of the (R)-Mosher ester; trans-stereoisomers were not separated.

Employing an S/C = 1000, a 99% ee coupled with a high conversion was obtained within 16 h for 1-indanone (S3), \(\alpha\)-tetralone (S4), and 4-chromanone (S5).

Shifting to functionalized variants, ATH of racemic 2- or 3-methoxycarbonyl-1-indanone (S6 and S7) using an S/C = 200 resulted in high diastereoselectivities (cis/trans 97:3 and 95:5, respectively) and 99% enantioselectivity indicating a dynamic kinetic resolution (DKR)\textsuperscript{12,13} occurring during their reduction. Regioisomeric methoxycarbonyl-\(\alpha\)-tetralones S8–S10 displayed as well an excellent ATH outcome. A high enantioselectivity (99% ee) was attained in all cases, with S8 undergoing DKR\textsuperscript{12} in 98:2 cis/trans ratio. Noteworthy, S9 exhibited some kinetic resolution (KR) during ATH as, at ~75% conversion, \textsuperscript{1}H NMR indicated a 60:40 cis/trans ratio.\textsuperscript{14} Most interestingly, in a related fashion to the reported DKR during ATH of readily enolizable \(\beta\)-keto esters (such as...
S6 and S8), a first-time DKR during reduction of a γ-keto ester as rac-3-methoxycarbonyl-1-indanone (S7) was encountered (Scheme 3). We hypothesize that this DKR occurs by keto-enol tautomerization of this 5-membered cyclic γ-keto ester via the racemization-prone dual benzylidene and allylic carbon. This stereolability could be accentuated in the transition state (TS) influenced by the electrostatic interaction as shown in Scheme 3. We assume that the configuration of the GC-detected trans-product (5.3%) is as depicted supported by the 99% ee obtained with 1-indanone (S3). By contrast, the 6-membered δ-keto ester higher homolog S10 is unable to undergo racemization (under the test conditions) of its methoxycarbonyl-borne benzylidene carbon precluding thus DKR.

The [Ru(TsDPEN)(η6-arene)]-catalyzed ATH mechanism was established by Noyori, Ikariya and co-workers who considered multiple CH...π attractive electrostatic interactions in the Ru(II)-hydride–ketone TS,24 in the case of racemic ketone S7, a more facile reduction of the (S)-enantiomer (vs. the (R)-enantiomer) is attributable to the CO2Me group outwards orientation minimizing the steric interference in the TS.

Conclusions

We have successfully prepared diastereo- and enantiopure syn- and anti-(α-aminobenzyl)-benzo-γ-sultam ligands 6 and explored them in Ru(II)-catalyzed ATH of conventional ketones in the presence of formic acid/triethylamine 5:2. The ATH rate and enantioselectivity using the syn isomer ligand were better than with the anti isomer. High enantioselectivities (99 to >99% ee) were obtained for the benzo-fused cyclic ketones S3–S10 based on 1-indanone or α-tetralone. Namely, a first-time ever DKR of a γ-keto carboxylic ester occurred during reduction. In fact, ketone S7 derived from 1-indanone afforded the corresponding γ-hydroxy ester in high cis/trans ratio (95:5) and excellent ee (99% ee for cis, >99% ee for trans).

Finally, this study is yet another example of how skeletal changes in a chiral ligand design can translate into unpredictable catalyst properties.

Experimental section

Materials and methods. The following non-commercial ketones were prepared according to literature procedures: 2-methoxycarbonyl-1-indanone25 and 2-methoxy-carbonyl-1-tetralone26 from 1-indanone and α-tetralone, respectively, using dimethyl carbonate; 3-methoxycarbonyl-1-indanone27 by esterification of 3-oxo-1-indanecarboxylic acid; 3-methoxycarbonyl-1-tetralone28 starting by a Stobbe condensation of benzaldehyde with dimethyl succinate; 4-methoxycarbonyl-1-tetralone29 from 2-phenyl-glutaric anhydride.

All reactions were conducted under an inert atmosphere (nitrogen or argon) using anhydrous solvents. HCO2H/Et3N 5:2 (azeotrope) was prepared by adding Et3N (280 mL, 2 mol) to HCO2H (190 mL, 5 mol) at 0 °C under nitrogen atmosphere and used as such. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F254 pre-coated plates (0.25 mm thickness); Rf values are reported and visualization was accomplished by irradiation with an UV lamp (254 nm) and/or staining with KMnO4 solution. Silica Gel 60 (40–63 μm) was used for flash column chromatography. 1H (299.9 MHz; internal Me2Si) and 13C (75.4 MHz; internal CDCl3) spectra were recorded for solutions in CDCl3 if not stated otherwise. HRMS measurements were obtained on a Q-TOF instrument equipped with an orthogonal Z-spray ESI interface.

Sodium (E)-2-β-styrylbenzenesulfonate (= sodium trans-o-stilbenesulfonate) [(E)-1]. To a freshly prepared solution of NaOMe in MeOH (80 mL, 54 mmol) was added 2-formylbenzenesulfonic acid sodium salt (10.20 g, 49.0 mmol) and the mixture cooled on an ice-bath. Following, benzyltriphenylphosphonium chloride (19.05 g, 49.0 mmol) in MeOH (50 mL) was added dropwise. The resulting pale yellow mixture was allowed to reach rt during 1 h and left to stir for 16 h. The mixture was concentrated and the residue suspended in cold H2O (50 mL). The solid was filtered, washed with cold H2O (20 mL) and CH2Cl2 until TLC showed no triphenylphosphine oxide present. After drying, a white powder (12.5 g) was obtained as an (E/Z)-isomeric mixture in 85:15 ratio. 1H NMR in DMSO-d6: δ 6.54 (d, J = 12.3 Hz) is the characteristic signal for the (Z)-isomer and δ 8.25 (d, J = 16.6 Hz) for the (E)-isomer. Recrystallization from MeCN to the title product as a white powder (8.14 g, 59% yield). 1H NMR (300 MHz, DMSO-d6): δ = 7.13 (d, 16.6 Hz, 1 H), 7.18–7.41 (m, 5 H), 7.50–7.53 (m, 2 H), 7.75–7.81 (m, 2 H), 8.25 (d, J = 16.6 Hz, 1 H). 13C NMR (76 MHz, DMSO-d6): δ = 125.3, 125.62, 125.58, 127.1, 127.5, 128.1, 128.2, 128.3, 128.7,
Sodium (E/Z)-2-[beta]-styrbylbenzenesulfonate [(E/Z)-1]. To a cold (0 °C) suspension of benzyltriphenylphosphonium chloride (11.67 g, 30 mmol) in THF (250 mL) was added dropwise under stirring NaHMDS (2 M in THF, 15 mL, 30 mmol). After stirring for 3 h at rt, the reaction mixture was cooled to −78 °C and a solution of 2-formylbenzenesulfonic acid sodium salt (6.25 g, 30 mmol) in MeOH (70 mL) was added dropwise. After 2 h, the mixture was allowed to reach rt and then concentrated. The residue was suspended in EtOAc/2-ProH (200 mL), filtered, and purified by column chromatography eluting with hexane/EtOAc/MeOH (7:2:1) then EtOAc/MeOH (4:1). Fractions containing the product/triphenylphosphine oxide were concentrated, and the solid suspended in H2O (400 mL) and stirred at rt for 3 h. The insoluble matter was filtered off and the filtrate concentrated and dried under high vacuum at 60 °C affording the title product (6.25 g, 91% yield) as a pale yellow powder.

(E)-2-[beta]-Styrbenzenesulfonamide [(E)-2]. To a cold (0 °C) suspension of (E)-1 (6.40 g, 22.68 mmol) in CH2Cl2 (160 mL) was added under stirring thionyl chloride (6.5 mL, 90 mmol) followed by DMF (50 μL). After heating at 50 °C for 5 h, the resulting solution was cooled to 0 °C and added dropwise to a cold (0 °C) solution of NH4OH (25%, 100 mL)/acetone (50 mL) keeping the internal temperature below 5 °C. Following, the mixture was stirred at 0 °C for 2 h, and CH2Cl2 (100 mL) and brine (50 mL) were added. The aqueous layer was re-extracted with CH2Cl2 (2 × 100 mL), and the combined organic layers were dried (Na2SO4) and concentrated. The crude was filtered through a bed of silica gel eluting with CH2Cl2/EtOAc (4:1). After concentration and trituration with iPr2O, the title product (5.17 g, 88%) was obtained as colorless crystals; mp 145–146 °C. H NMR (300 MHz, CDCl3): δ = 7.42 (s, 2 H), 7.07 (d, J = 16 Hz, 1 H), 7.28–7.51 (m, 4 H), 7.50–7.65 (m, 3 H), 7.73 (d, J = 16 Hz, 1 H), 7.97 (d, J = 16 Hz, 1 H), 8.07 (dd, d = 8, 1 Hz, 1 H). \(^{13}C\) NMR (76 MHz, CDCl3): δ = 124.4, 127.1, 127.5, 128.0, 128.2, 128.7, 133.0, 134.6, 136.3, 136.5, 138.9. HRMS–ESI (m/z): [M + H]+ calcld for C14H12NO2S, 260.0745; found, 260.0748.

(E/Z)-[beta]-Styrbenzenesulfonamide [(E/Z)-2]. Prepared from (E/Z)-1 (1:1) (4.00 g, 14.18 mmol) following a similar procedure as for (E)-2. The title product (3.17 g, 86% yield; E/Z ~1:1) was obtained as an amber-colored oil.

trans-o-Sulfamoyl-stilbene oxide (trans-3). To a solution of (E)-2 (4.50 g, 17.36 mmol) in CH2Cl2 (50 mL) was added at rt a solution of m-CPBA (5.00 g, 77%), dried over MgSO4 in CH2Cl2 (50 mL). After stirring for 16 h, the mixture was washed with sat. aq NaHCO3 (2 × 100 mL). The organic phase was filtered through a bed of silica gel/Na2SO4 and concentrated affording the title product (4.59 g, 96% yield) as a slightly yellowish syrup which crystallized upon standing; mp 86–89 °C. H NMR (300 MHz, CDCl3): δ = 3.88 (d, J = 2 Hz, 1 H), 4.62 (d, J = 2 Hz, 1 H), 4.87 (br s, 2 H), 7.34–7.51 (m, 6 H), 7.57–7.71 (m, 2 H), 8.04 (d, J = 8 Hz, 1 H). \(^{13}C\) NMR (76 MHz, CDCl3): δ = 59.9, 62.3, 125.7, 126.8, 128.0, 128.2, 128.8, 133.1, 135.5, 136.0, 140.0. HRMS–ESI (m/z): [M + H]+ calcld for C14H12NO2S, 276.0694; found, 276.0689.

trans-4-Hydroxy-3-phenyl-1,1-dioxo-benzo-1,2-thiazine (trans-4). To a cold (0 °C) solution of trans-3 (2.00 g, 7.26 mmol) in MeOH (30 mL) was added a freshly prepared solution of LiOMe in MeOH (0.5 M, 14.8 mL, 7.4 mmol) and the resulting solution allowed to reach rt. After heating at 55 °C for 2 h, it was brought to rt and the concentrated residue was partitioned between CH2Cl2 (100 mL) and 0.5 M HCl (40 mL). The aq layer was re-extracted with CH2Cl2 (20 mL), and the combined organic layers were filtered through a bed of silica gel/Na2SO4 and concentrated affording the title product (1.94 g, 97% yield) as a white crispy foam. The structure is supported by \(^1H\),\(^{13}C\)-HMBC analysis from a correlation between the proximal aromatic hydrogen of the 1,1-dioxo-benzo-1,2-thiazine core and the carbon atom bearing the hydroxyl group (see the Supporting Information). H NMR (300 MHz, CDCl3): δ = 2.30 (d, J = 6 Hz, 1 H), 4.56–4.68 (m, 1 H), 4.92 (d, J = 9 Hz, 1 H), 5.12 (d, J = 10 and 5 Hz, 1 H), 7.41–7.55 (m, 6 H), 7.60–7.70 (m, 1 H), 7.77–7.83 (m, 1 H), 7.86 (dd, J = 8 and 1 Hz, 1 H). \(^{13}C\) NMR (76 MHz, CDCl3): δ = 63.7, 69.8, 123.0, 126.8, 127.7, 128.4, 129.1, 129.2, 132.6, 137.1, 137.3, 137.4. HRMS–ESI (m/z): [M + H]+ calcld for C14H12NO2S, 276.0694; found, 276.0690.

trans-2,3-Benzylidene-1,1-dioxo-benzo-1,2-thiazolidine (trans-5). To a cold (0 °C) solution of trans-4 (1.50 g, 5.45 mmol) in THF (30 mL) was added Et3N (1.7 mL, 12 mmol) followed by dropwise addition of methane sulfonyl chloride (0.69 g, 6.60 mmol). The resulting white suspension was left to stir at 0 °C for 0.5 h then at rt for 1 h. The mixture was quenched at 0 °C with H2O (20 mL), EtOAc (20 mL) was added and layers were separated. The aq layer was re-extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried (Na2SO4) and concentrated. The crude was purified on silica gel eluting with petroleum ether (40–60)/EtOAc (9:1, 8:2, 7:3 then 6:4) followed by a plug of silica gel eluting with CH2Cl2. The resulting mixture was stirred at 40 °C for 4 h, brought to rt and filtered through a plug of silica gel eluting with CH2Cl2. The crude was purified on silica gel eluting with toluene/EtOAc (24:1) affording the title product (1.52 g, 76% yield) as an oil. cis-5: \(^1H\) NMR (300 MHz, CDCl3): δ = 4.31 (d, J = 5 Hz, 1 H), 4.62 (d, J = 5 Hz, 1 H),...
6.92–7.02 (m, 2 H), 7.03–7.21 (m, 3 H), 7.35–7.52 (m, 2 H), 7.61–7.70 (m, 1 H), 7.71–7.82 (m, 1 H). 13C NMR (76 MHz, CDCl3): δ = 47.3, 55.8, 122.5, 126.4, 127.2, 127.8, 128.5, 130.3, 131.0, 133.2, 134.1, 137.1. HRMS–ESI (m/z): [M + H]+ calcld for C19H19NO3S = 358.1044; found, 358.1055.

syn-3-(a-Aminobenzyl)-1,1-dioxo-benzo-1,2-thiazolidine (syn-6). A solution of trans-5 (910 mg, 3.53 mmol) and NaN3 (0.56 g, 8.56 mmol) in MeCN/H2O (4:1, 30 mL) was heated at 55 °C for 1 h, then brought to rt and concentrated. The residue was partitioned between H2O (pH 4.5) and CH2Cl2, and the combined organic layers were dried (Na2SO4) and concentrated. The resulting oil (1.3 g) in EtOAc (30 mL), 5% Pd/C (130 mg) was added and the mixture was hydrogenated using Parr apparatus at 20 psig H2 for 1 h. After filtration through Celite and concentration, the residue was purified on silica gel eluting successively with CH2Cl2, CH2Cl2/EtOAc (4:1 then 1:2) and EtOAc/EtOH (4:1), affording syn-6 (910 mg, 94% yield) as a yellowish syrup. 1H NMR (300 MHz, CDCl3): δ = 2.11 (br s, 3 H), 4.36 (d, J = 6 Hz, 1 H), 4.90 (d, J = 6 Hz, 1 H), 7.02–7.19 (m, 1 H), 7.28–7.62 (m, 7 H), 7.66–7.86 (m, 1 H). 13C NMR (76 MHz, CDCl3): δ = 59.0, 63.1, 121.4, 125.8, 127.4, 127.8, 128.2, 129.6, 132.5, 136.3, 136.7, 140.6. HRMS–ESI (m/z): [M + H]+ calcld for C19H19NO3S = 358.1055; found, 358.1044.

The syn-6 enantiomers were separated by preparative HPLC on ChiralPak IC (5 μm, 250 × 30 mm), mobile phase CH2Cl2/EtOH (98:2), flow rate 42.5 mL/min, 25 °C, UV detection at 280 nm. Analytical HPLC conditions: ChiralPak IC (5 μm, 250 × 46 mm), mobile phase: CH2Cl2/EtOH (98:2), flow rate: 1 mL/min, 25 °C, UV detection at 230 nm. 21

1st eluting syn enantiomer (3R,1’S)-6: beige-colored powder, 373 mg (40%); tR 15.9 min; >99% ee; [α]D 21 +11.5 (c 1.0 in CHCl3); chemical purity (area at 230 nm) = 96.9%. The indicated absolute configuration was determined by X-ray analysis of the (1S)-camphor-10-sulfonic acid salt (colorless plates from MeOH).

2nd eluting syn enantiomer (3R,1’R)-6: beige-colored powder, 373 mg (38%); tR 26.9 min; >99% ee; [α]D 22 +11.6 (c 1.0 in CHCl3); chemical purity (area at 230 nm) = 93.3%.

anti-3-(a-Aminobenzyl)-1,1-dioxo-benzo-1,2-thiazolidine (anti-6). Prepared from cis-5 (1.10 g, 4.27 mol) following a similar procedure as for syn-6. The title compound (1.06 g, 90% yield) was obtained as a yellowish orange-colored solution of the catalyst was used directly in ATH without back-filling and stirred at 40 °C for 1 h. The resulting orange-colored solution of the catalyst was used directly in ATH or was concentrated to dryness when the ATH was performed in neat HCO2H/Et2N 5:2.

ATH of ketones. To the above preformed solution of [RuCl2(ligand 6)](n-arene) (complex (1 ml; with S/C = 100: 0.01 mmol Ru atom; with S/C = 200: 0.005 mmol Ru atom; with S/C = 1000: 0.001 mmol Ru atom) was added HCO2H/Et2N 5:2 (250 μL; 500 μL when no cosolvent was used) followed by the ketone (1.0 mmol). This mixture was stirred at 40 °C with continuous mild N2 sweeping. The reaction progress was monitored by 1H NMR. Workup: the reaction mixture was partitioned between Et2O (5 mL) and H2O (5 mL). The aq layer was re-extracted with Et2O (5 mL) and the combined organic layers were filtered through a bed of silica gel/Na2SO4, and concentrated.

Preparation of racemic alcohol standards. Samples of the racemic alcohols were prepared by reduction of the corresponding ketones with NaBH4 (3 equiv) in MeOH (2 mL in the case of ethyl benzoylacetate) at 0 °C to rt. Workup: H2O was added, the mixture neutralized with aq HCl, and the product extracted with Et2O. The Et2O layer was successively washed with H2O and brine, filtered through a bed of silica gel/Na2SO4, and concentrated.

Characterization and ee determination of the ATH prepared chiral alcohols. 23

(R)-1-Phenylethanol. Colorless oil (117 mg, 96% yield); 78% ee. 1H NMR (300 MHz, CDCl3): δ = 1.47 (d, J = 6.4 Hz, 3 H), 2.04 (br s, 1 H), 4.86 (q, J = 6.4 Hz, 1 H), 7.35–7.37 (m, 3 H). Ee was determined by chiral GC analysis 23b on Chiralsil-DEX CB column (25 m × 0.25 mm), 120 °C (isothermal), tR 4.6 min (R), 4.8 min (S).

Ethyl (R)-3-hydroxy-3-phenylpropionate. Colorless oil (190 mg, 98% yield); 92% ee. 1H NMR (300 MHz, CDCl3): δ = 1.27 (t, J = 7.2 Hz, 3 H), 2.65–2.83 (m, 2 H), 3.00 (q, J = 7.2 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 5.14 (dd, J = 8.3 and 4.5 Hz, 1 H), 7.28–7.42 (m, 5 H). Ee was determined by chiral GC analysis 23b on Chiralsil-DEX CB (25 m × 0.25 mm), 140 °C (isothermal); tR 14.6 min (S), 14.9 min (R).

(R)-1-Indanol. Colorless oil which crystallized upon standing (130 mg, 97% yield); 99% ee. 1H NMR (300 MHz, CDCl3): δ = 1.75 (br s, 1 H), 1.86–2.02 (m, 1 H), 2.41–2.58 (m, 4 H), 3.44–3.48 (m, 2 H), 6.91–7.00 (m, 1 H), 7.04–7.05 (m, 1 H)
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2.33 (app t, 3 H, 1 H), 3.06 (m, J = 15.9, 8.5, 4.8 Hz, 1 H), 5.25 (t, J = 6.0 Hz, 1 H), 7.17–7.26 (m, 3 H), 7.33–7.47 (m, 1 H). Ee was determined by chiral HPLC analysis on Chiralpak IB-3 column (25 cm). Eluent hexane/2-ProH (97:3), flow rate 1.0 mL/min, UV detection at 220 nm; racemates (mixture prepared by weighing both corresponding ATH products derived from enantiomeric catalysts): tR 15.4 min (trans-1), 17.4 min [cis-(R,R)], 19.7 min (trans-2), 32.7 min [cis-(S,S)].

(1R,3R)-3-Methoxycarbonyl-1-tetralol. Light violet-colored syrup (204 mg, 99% yield); cis/trans = 50:50 by 1H NMR; 99% ee (cis). 1H NMR (300 MHz, CDCl3): δ = 1.70 (br s, 1 H), 2.75–2.99 (m, 4 H), 3.70 (s, 3 H), 4.80 (d, J = 9.0 Hz, CH, trans diastereomer), 5.05 (m, 1 H), 7.12–7.14 (m, 1 H), 7.19–7.25 (m, 2 H), 7.37–7.42 (m, 1 H). Ee was determined by chiral HPLC analysis on Chiralpak IB-3 column (25 cm). Eluent hexane/2-ProH (97:3), flow rate 1.0 mL/min, UV detection at 220 nm; racemates (mixture prepared by weighing both corresponding ATH products derived from enantiomeric catalysts): tR 15.4 min (trans-1), 17.4 min [cis-(R,R)], 19.7 min (trans-2), 32.7 min [cis-(S,S)].

Notes and references


A preparation of enantiomeric 3-ethoxycarbonyl-1-indanone (96%) ee by asymmetric hydrogenation of \( \text{oxoformyl-acid methyl ester using \{Rh[\text{BINAP}]} \text{ClO}_4 \) has been achieved. For this, see: K. Kündu, J. V. McCullagh and A. T. Morehead, Jr., \textit{J. Am. Chem. Soc.}, 2005, 127, 16042–16043.


Separation of rac syn-6 enantiomers by preparative HPLC was outsourced to Chiral Technologies Europe (France).

Separation of rac anti-6 enantiomers by preparative SFC was outsourced to WuXi AppTec Co., Ltd (China).

For chiral GC analysis, see: (a) ref. Se. (b) ref. 3b.

‡ CCDC-1436151 [for syn-(3S,1'R)-6'(S)-CSA], CCDC-1436152 [for anti-(3R,1'R)-6'(R)-CSA], CCDC-1436153 [for trans-5], and CCDC-1436154 [for S7-reduced] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk request cif.

